

DEFEROXAMINE MESYLATE - deferoxamine mesylate injection, powder, lyophilized, for solution

Barr Laboratories Inc.

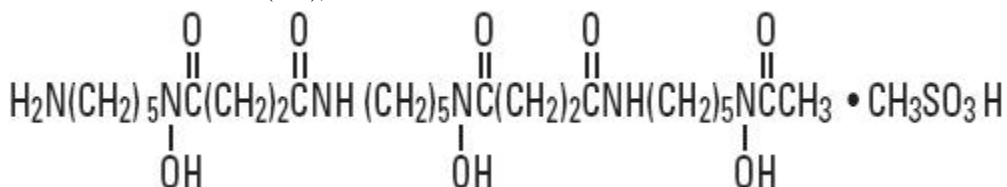
Fliptop Vials

For subcutaneous, intramuscular or intravenous administration.

Rx only

DESCRIPTION

Deferoxamine mesylate for injection, USP, is an iron-chelating agent, available in vials for intramuscular, subcutaneous, and intravenous administration. Deferoxamine mesylate is supplied as vials containing 500 mg and 2 g of deferoxamine mesylate USP in sterile, lyophilized form. Deferoxamine mesylate is N-[5-[3-[(5-Aminopentyl)hydroxycarbonyl]propionamido]pentyl]-3-[[5-(N-hydroxyacetamido)pentyl]carbamoyl]propionohydroxamic acid monomethanesulfonate (salt), and its structural formula is:



Deferoxamine mesylate USP is a white to off-white powder. It is freely soluble in water and slightly soluble in methanol. Its molecular weight is 656.79. The molecular formula is $\text{C}_{25}\text{H}_{48}\text{N}_6\text{O}_8 \cdot \text{CH}_4\text{O}_3\text{S}$.

CLINICAL PHARMACOLOGY

Deferoxamine mesylate chelates iron by forming a stable complex that prevents the iron from entering into further chemical reactions. It readily chelates iron from ferritin and hemosiderin but not readily from transferrin; it does not combine with the iron from cytochromes and hemoglobin. Deferoxamine mesylate does not cause any demonstrable increase in the excretion of electrolytes or trace metals. Theoretically, 100 parts by weight of deferoxamine mesylate is capable of binding approximately 8.5 parts by weight of ferric iron.

Deferoxamine mesylate is metabolized principally by plasma enzymes, but the pathways have not yet been defined. The chelate is readily soluble in water and passes easily through the kidney, giving the urine a characteristic reddish color. Some is also excreted in the feces via the bile.

INDICATIONS AND USAGE

Deferoxamine mesylate for injection is indicated for the treatment of acute iron intoxication and of chronic iron overload due to transfusion-dependent anemias.

Acute Iron Intoxication

Deferoxamine mesylate is an adjunct to, and not a substitute for, standard measures used in treating acute iron intoxication, which may include the following: induction of emesis with syrup of ipecac; gastric lavage; suction and maintenance of a clear airway; control of shock with intravenous fluids, blood, oxygen, and vasopressors; and correction of acidosis.

Chronic Iron Overload

Deferoxamine mesylate can promote iron excretion in patients with secondary iron overload from multiple transfusions (as may occur in the treatment of some chronic anemias, including thalassemia). Long-term therapy with deferoxamine mesylate slows accumulation of hepatic iron and retards or eliminates progression of hepatic fibrosis.

Iron mobilization with deferoxamine mesylate is relatively poor in patients under the age of 3 years with relatively little iron overload. The drug should ordinarily not be given to such patients unless significant iron mobilization (e.g., 1 mg or more of iron per day) can be demonstrated.

Deferoxamine mesylate is not indicated for the treatment of primary hemochromatosis, since phlebotomy is the method of choice for removing excess iron in this disorder.

CONTRAINDICATIONS

Deferoxamine mesylate is contraindicated in patients with severe renal disease or anuria, since the drug and the iron chelate are excreted primarily by the kidney (See WARNINGS).

WARNINGS

Ocular and auditory disturbances have been reported when deferoxamine mesylate was administered over prolonged periods of time, at high doses, or in patients with low ferritin levels. The ocular disturbances observed have been blurring of vision; cataracts after prolonged administration in chronic iron overload; decreased visual acuity including visual loss, visual defects, scotoma; impaired peripheral, color, and night vision; optic neuritis, cataracts, corneal opacities, and retinal pigmentary abnormalities. The auditory abnormalities reported have been tinnitus and hearing loss including high frequency sensorineural hearing loss. In most cases, both

ocular and auditory disturbances were reversible upon immediate cessation of treatment (see PRECAUTIONS/Information for Patients and ADVERSE REACTIONS/Special Senses).

Visual acuity tests, slit-lamp examinations, funduscopy and audiometry are recommended periodically in patients treated for prolonged periods of time. Toxicity is more likely to be reversed if symptoms or test abnormalities are detected early.

High doses of deferoxamine mesylate and concomitant low ferritin levels have also been associated with growth retardation. After reduction of deferoxamine mesylate dose, growth velocity may partially resume to pretreatment rates (see PRECAUTIONS/Pediatric Use).

Adult respiratory distress syndrome, also reported in children, has been described following treatment with excessively high intravenous doses of deferoxamine mesylate in patients with acute iron intoxication or thalassemia.

PRECAUTIONS

General

Flushing of the skin, urticaria, hypotension, and shock have occurred in a few patients when deferoxamine mesylate was administered by rapid intravenous injection. THEREFORE, DEFEROXAMINE MESYLATE SHOULD BE GIVEN INTRAMUSCULARLY OR BY SLOW SUBCUTANEOUS OR INTRAVENOUS INFUSION.

Iron overload increases susceptibility of patients to *Yersinia enterocolitica* and *Yersinia pseudotuberculosis* infections. In some rare cases, treatment with deferoxamine mesylate has enhanced this susceptibility, resulting in generalized infections by providing this bacteria with a siderophore otherwise missing. In such cases, deferoxamine mesylate treatment should be discontinued until the infection is resolved.

In patients receiving deferoxamine mesylate, rare cases of mucormycosis, some with a fatal outcome, have been reported. If any of the suspected signs or symptoms occur, deferoxamine mesylate should be discontinued, mycological tests carried out and appropriate treatment instituted immediately.

In patients with severe chronic iron overload, impairment of cardiac function has been reported following concomitant treatment with deferoxamine mesylate and high doses of vitamin C (more than 500 mg daily in adults). The cardiac dysfunction was reversible when vitamin C was discontinued. The following precautions should be taken when vitamin C and deferoxamine mesylate are to be used concomitantly:

- Vitamin C supplements should not be given to patients with cardiac failure.
- Start supplemental vitamin C only after an initial month of regular treatment with deferoxamine mesylate.
- Give vitamin C only if the patient is receiving deferoxamine mesylate regularly, ideally soon after setting up the infusion pump.
- Do not exceed a daily Vitamin C dose of 200 mg in adults, given in divided doses.
- Clinical monitoring of cardiac function is advisable during such combined therapy.

In patients with aluminum-related encephalopathy, high doses of deferoxamine mesylate may exacerbate neurological dysfunction (seizures), probably owing to an acute increase in circulating aluminum. Deferoxamine mesylate may precipitate the onset of dialysis dementia. Treatment with deferoxamine mesylate in the presence of aluminum overload may result in decreased serum calcium and aggravation of hyperparathyroidism.

Drug Interactions

Vitamin C: Patients with iron overload usually become vitamin C deficient, probably because iron oxidizes the vitamin. As an adjuvant to iron chelation therapy, vitamin C in doses up to 200 mg for adults may be given in divided doses, starting after an initial month of regular treatment with deferoxamine mesylate (see PRECAUTIONS). Vitamin C increases availability of iron for chelation. In general, 50 mg daily suffices for children under 10 years old and 100 mg daily for older children. Larger doses of vitamin C fail to produce any additional increase in excretion of iron complex.

Prochlorperazine: Concurrent treatment with deferoxamine mesylate and prochlorperazine, a phenothiazine derivative, may lead to temporary impairment of consciousness.

Gallium-67: Imaging results may be distorted because of the rapid urinary excretion of deferoxamine mesylate-bound gallium-67. Discontinuation of deferoxamine mesylate 48 hours prior to scintigraphy is advisable.

Information for Patients

Patients experiencing dizziness or other nervous system disturbances, or impairment of vision or hearing, should refrain from driving or operating potentially hazardous machines (see ADVERSE REACTIONS).

Patients should be informed that occasionally their urine may show a reddish discoloration.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term carcinogenicity studies in animals have not been performed with deferoxamine mesylate.

Cytotoxicity may occur, since deferoxamine mesylate has been shown to inhibit DNA synthesis *in vitro*.

Pregnancy Category C

Delayed ossification in mice and skeletal anomalies in rabbits were observed after deferoxamine mesylate was administered in daily doses up to 4.5 times the maximum daily human dose. No adverse effects were observed in similar studies in rats.

There are no adequate and well-controlled studies in pregnant women. Deferoxamine mesylate should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when deferoxamine mesylate is administered to a nursing woman.

Pediatric Use

Pediatric patients receiving deferoxamine mesylate should be monitored for body weight and growth every 3 months.

Safety and effectiveness in pediatric patients under the age of 3 years have not been established (see INDICATIONS AND USAGE, WARNINGS, PRECAUTIONS/Drug Interactions/Vitamin C, and ADVERSE REACTIONS).

ADVERSE REACTIONS

The following adverse reactions have been observed, but there are not enough data to support an estimate of their frequency.

At the Injection Site: localized irritation, pain, burning, swelling, induration, infiltration, pruritus, erythema, wheal formation, eschar, crust, vesicles, local edema. Injection site reactions may be associated with systemic allergic reactions (see Body as a Whole, below).

Hypersensitivity Reactions and Systemic Allergic Reactions: generalized rash, urticaria, anaphylactic reaction with or without shock, angioedema.

Body as a Whole: Local injection site reactions may be accompanied by systemic reactions like arthralgia, fever, headache, myalgia, nausea, vomiting, abdominal pain, or asthma.

Rare infections with *Yersinia* and *Mucormycosis* have been reported in association with deferoxamine mesylate use (see PRECAUTIONS).

Cardiovascular: tachycardia, hypotension, shock.

Digestive: abdominal discomfort, diarrhea, nausea, vomiting.

Hematologic: blood dyscrasia (e.g., Cases of thrombocytopenia and/or leukopenia have been reported. A causal relationship has not been clearly established.)

Musculoskeletal: Leg cramps. Growth retardation and bone changes (e.g., metaphyseal dysplasia) are common in chelated patients given doses above 60 mg/kg, especially those who begin iron chelation in the first three years of life. If doses are kept to 40 mg/kg or below, the risk may be reduced (see WARNINGS, PRECAUTIONS/Pediatric Use).

Nervous system: neurological disturbances including dizziness, peripheral sensory, motor, or mixed neuropathy, paresthesias; exacerbation or precipitation of aluminum-related dialysis encephalopathy (see PRECAUTIONS/Information for Patients).

Special Senses: High-frequency sensorineural hearing loss and/or tinnitus are uncommon if dosage guidelines are not exceeded and if dose is reduced when ferritin levels decline. Visual disturbances are rare if dosage guidelines are not exceeded. These may include decreased acuity, blurred vision, loss of vision, dyschromatopsia, night blindness, visual field defects, scotoma, retinopathy (pigmentary degeneration), optic neuritis, and cataracts (see WARNINGS).

Respiratory: acute respiratory distress syndrome (with dyspnea, cyanosis, and/or interstitial infiltrates) (see WARNINGS).

Skin: very rare generalized rash.

Urogenital: dysuria, impaired renal function (see CONTRAINDICATIONS).

OVERDOSAGE

Acute Toxicity

Intravenous LD₅₀S (mg/kg): mice, 287; rats, 329.

Signs and Symptoms

Inadvertent administration of an overdose or inadvertent intravenous bolus administration/rapid intravenous infusion may be associated with hypotension, tachycardia and gastrointestinal disturbances; acute but transient loss of vision, aphasia, agitation, headache, nausea, pallor, CNS depression including coma, bradycardia and acute renal failure have been reported.

Treatment

There is no specific antidote. Deferoxamine mesylate should be discontinued and appropriate symptomatic measures undertaken. Deferoxamine mesylate is readily dialyzable.

DOSAGE AND ADMINISTRATION

Preparation of Solution

Deferoxamine mesylate is preferably dissolved by adding 5 mL of Sterile Water for Injection to each 500 mg vial or 20 mL of Sterile Water for Injection to each 2 g vial. The reconstituted deferoxamine mesylate solution is isotonic, clear and colorless to slightly yellowish at the recommended concentration of 10%.

In clinical situations requiring a smaller volume of solution (e.g., intramuscular injection), deferoxamine mesylate may be dissolved by adding 2 mL of Sterile Water for Injection to each 500 mg vial or 8 mL of Sterile Water for Injection to each 2 g vial. This concentration may produce a stronger yellow-colored solution. The drug should be completely dissolved before the solution is withdrawn.

Preparation of the above reconstituted solutions results in a final volume that is greater than the specified volume of Sterile Water added.

Note: Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Deferoxamine mesylate reconstituted with Sterile Water for Injection **IS FOR SINGLE USE ONLY.**

The product should be used immediately after reconstituting (commencement of treatment within 3 hours) for microbiological safety. When reconstitution is carried out under validated aseptic conditions (in a sterile laminar flow hood using aseptic technique), the product may be stored at room temperature for a maximum period of 24 hours before use. Do not refrigerate reconstituted solution. Reconstituting deferoxamine mesylate in solvents or under conditions other than indicated may result in precipitation. Turbid solutions should not be used.

Acute Iron Intoxication

Intramuscular Administration

This route is preferred and should be used for ALL PATIENTS NOT IN SHOCK.

Dosage. See Preparation of Solution, above. A dose of 1000 mg should be administered initially. This may be followed by 500 mg every 4 hours for two doses. Depending upon the clinical response, subsequent doses of 500 mg may be administered every 4-12 hours. The total amount administered should not exceed 6000 mg in 24 hours.

Intravenous Administration

THIS ROUTE SHOULD BE USED ONLY FOR PATIENTS IN A STATE OF CARDIOVASCULAR COLLAPSE AND THEN ONLY BY SLOW INFUSION. THE RATE OF INFUSION SHOULD NOT EXCEED 15 MG/KG/HR FOR THE FIRST 1000 MG ADMINISTERED. SUBSEQUENT IV DOSING, IF NEEDED, MUST BE AT A SLOWER RATE, NOT TO EXCEED 125 MG/HR.

Dosage. See Preparation of Solution, above.

The reconstituted solution is added to physiologic saline, glucose in water, or Ringer's lactate solution.

An initial dose of 1000 mg should be administered at a rate NOT TO EXCEED 15 mg/kg/hr. This may be followed by 500 mg over 4 hours for two doses. Depending upon the clinical response, subsequent doses of 500 mg may be administered over 4-12 hours. The total amount administered should not exceed 6000 mg in 24 hours.

As soon as the clinical condition of the patient permits, intravenous administration should be discontinued and the drug should be administered intramuscularly.

Chronic Iron Overload

The more effective of the following routes of administration must be chosen on an individual basis for each patient.

Intramuscular Administration

See Preparation of Solution, above. A daily dose of 500-1000 mg should be administered intramuscularly. In addition, 2000 mg should be administered intravenously with each unit of blood transfused; however, deferoxamine mesylate should be administered separately from the blood. The rate of intravenous infusion must not exceed 15 mg/kg/hr. The total daily dose should not exceed 1000 mg in the absence of a transfusion, or 6000 mg even if transfused three or more units of blood or packed red blood cells.

Subcutaneous Administration

See Preparation of Solution, above. A daily dose of 1000-2000 mg (20-40 mg/kg/day) should be administered over 8-24 hours, utilizing a small portable pump capable of providing continuous mini-infusion. The duration of infusion must be individualized. In some patients, as much iron will be excreted after a short infusion of 8-12 hours as with the same dose given over 24 hours.

HOW SUPPLIED

Vials – each containing 500 mg of sterile, lyophilized deferoxamine mesylate

Cartons of 4 vials.....NDC 0555-1132-12

Vials – each containing 2 g of sterile, lyophilized deferoxamine mesylate

Cartons of 4 vials.....NDC 0555-1131-11

Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.]

For single use only.

Discard unused portion.

Revised: **MAY 2007**

Manufactured by Hospira Inc.

Lake Forest, IL 60045

for **BARR LABORATORIES, INC.**

Pomona, NY 10970



PRINCIPAL DISPLAY PANEL

Fliptop Vial For single use only, NDC 0555-1132-12

Deferoxamine Mesylate
for Injection, USP

500 mg Rx only

See package brochure for reconstituted storage and expiry. Turbid solutions should not be used. Store at 20° to 25°C [See USP]. Discard unused portion.

For S.C., I.M. or I.V. Use

Mfg. for BARR LABORATORIES, INC., Pomona, NY 10970

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DB110L-01 R5-07 v.1

500 mg Vial Label Text

Fliptop Vial For single use only. NDC 0555-1132-12

Deferoxamine Mesylate
for Injection, USP

500 mg

Rx only

See package brochure for reconstituted storage and expiry.

Turbid solutions should not be used. Store at 20° to 25°C [See USP]. Discard unused portion.

For S.C., I.M. or I.V. Use

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PRINCIPAL DISPLAY PANEL

Fliptop Vial

Deferoxamine Mesylate
for Injection, USP

2 g Rx only

See package brochure for reconstituted storage and expiry. Turbid solutions should not be used. Store at 20° to 25°C [See USP]. Discard unused portion.

For single use only.
For S.C., I.M. or I.V. Use

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Mfg. for BARR LABORATORIES, INC.
Pomona, NY 10970

NDC 0555-1131-11

DB125L-01 R5-07 v.1

2 g Vial Label Text

Fliptop Vial NDC 0555-1131-11

Deferoxamine Mesylate
for Injection, USP

2 g

Rx only

See package brochure for
reconstituted storage and expiry.
Turbid solutions should not be
used. Store at 20° to 25°C [See
USP]. Discard unused portion.

For single use only.

For S.C., I.M. or I.V. Use

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Pomona, NY 10970

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